The new rejection is based on §103, whereby claims 10 and 15-19 are rejected as obvious from Peeters in view of newly cited and applied Miller et al, reference V (Miller). The rejection is respectfully traversed.

Applicants believe and respectfully but strongly submit that consideration of the prior art "as a whole" as is required under the law would have provided the person of ordinary skill in the art no reasonable likelihood that applicants' invention would succeed, and this is pointed out for the reasons set forth below. A reasonable likelihood of success is one of the minimum requirements of a *prima facie* case of obviousness, MPEP 2143.

In relying on Peeters in view of Miller, the rejection states as follows regarding Peeters:

> Peeters teaches the compound designated GM 611, the compound that is administered in the present claims to be a motilin receptor agonist with potential as a prokinetic agent.
>
> See the discussion under Current Opinion on pages 556, where administration of a therapeutic agent such as a motilin receptor agonist, to treat hypomotility disorders, such as constipation, is clearly suggested.

However, in Peeters, reference to constipation appears only in the following phrase:

> "The number of therapeutic agents available to treat hypomotility disorders such as gastroparesis,

> pseudo-obstruction and constipation is limited." (Page 556, left column, lines 21-23).

Thus the above quoted language from the Office Action is out of context with the disclosure of Peeters.

It is clear that the therapeutic agent referred to in the phrase referring to constipation quoted above from Peeters does not include motilides, since no motilides had been granted marketing authorization in any countries by the priority date of the instant application.

Peeters also describes that motilides may have potential as prokinetic agents (page 556, left column, lines 26-30), but there is no description in the Peeters document that motilides could be applied to treatment of constipation.

Further, it is clear that at the priority date of the present application, a person highly skilled in the art could not have predicted whether motilides could be applied in treating constipation, since motilides have a completely different mechanism of action than existing therapeutic agents for that purpose, which is pointed out in Peeters on page 556, left column, lines 26-27.

In addition, Peeters includes the following disclosure:

> "Moreover, the parent compound, the well-known antibiotic erythromycin, has been used successfully for a variety of

> clinical conditions, although it is less potent than the newer motilides such as GM-611." (Page 556, left column, lines 30-33).

Namely, this phrase refers to erythromycin that is also known as motilide. However, the fact that erythromycin has no effect on colon motility had been disclosed in non-patent documents, which are referred to in the subject specification and have been submitted to the USPTO.

For example, Bradette et al (J. Gastrointest Mot. 1993, 5, 247-251), copy attached, discloses their experimental results of colonic contractile activity by administration of erythromycin (200 mg, i.v.) and the supraphysiological dose of motilin (100 ng $kg^{-1}$ i.v.) to humans. The document describes that on the more proximal segments of the colon, motilin and erythromycin were inactive, and that when both agents were administered during the digestive period, both failed to modify the contractile stimulation normally seen in all regions of the colon after meal (page 247, Abstract).

Further, Jameson et al (Aliment, Pharmacol. Ther. 1992, 6, 589-595), copy attached, also describes that oral intravenous administration of erythromycin has no effect on human distal colonic motility (page 589, Abstract), and includes the following description:

> "Erythromycin, in doses known to affect upper gastrointestinal and gall bladder

> motility, has no effect on either distal colonic pressure activity or colonic transit times in normal subject. This suggests the motilin receptors may be absent in the human colon and the therapeutic potential of erythromycin and its analogues may be limited to dysmotility affecting the proximal gut only." (Page 594, lines 38-42).

In addition, Bassotti et al (Z. Gastroenterol. 1998, 36, 209-213), copy attached, discloses study results with 18 severly constipated women, who were randomized to receive a dose of erythromycin, and concludes that erythromycin cannot be considered a colokinetic agent, at least as doses commonly employed in the upper gut (page 209, summary).

In light of the prior art disclosed in these documents, a person skilled in the art would naturally have considered that GM-611 would likely have no effect on the colonic motility as the parent compound, erythromycin also has no effect, and therefore that GM-611 cannot reasonably be expected to succeed in the treatment of constipation, and thus cannot be applied to the treatment of constipation.

In light of the foregoing, although Peeters suggests that application of GM-611 to gastroparesis (page 556, right column, lines 1-21), this document includes neither any

description nor suggestion regarding application of GM-611 to constipation.

Therefore applicants believe that the statement in the rejection of "administration of a therapeutic agent such as a motilin receptor agonist, to treat hypomotility disorders, such as constipation, is clearly suggested" in Peeters is based on a misunderstanding or is an unwarranted extrapolation from what Peeters actually describes.

To supplement Peeters, the Office Action states regarding Miller as follows:

"Miller teaches motilin receptors exist in abundance in the colon, and motilin agonists, of which GM-611 is taught to be an example, are desirable for the treatment of hypokinetic disorders. See the first and third paragraphs in the Introduction."

Applicants note that Miller includes the following phrases in the Introduction section: "we now know that motilin receptors exist in abundance in the colon." (Page 283, lines 12-13). However, the document only discloses a specific reference to motilin receptors present in the rabbit colon. Further, Miller also refers to the difference of motilin receptors between species as follows:

> "More recently, when working with human tissues, we could observe species heterogeneity (between rabbit and man) in the pharmacological (and probably

structural) characteristics of the motilin receptor" (page 286, lines 26-29).

Regarding the difference of motilin receptors between species, Strunz et al (Gastroenterology 68, 1485-1491, 1975), copy attached, discloses that strips of circular muscle of descending colon, sigmoid colon, and rectum proved unresponsive even to 0.5 X $10^{-6}$ of 13-norleucine motilin, which is biologically equivalent to motilin (page 1488, right column, lines 1-6), while circular muscle of descending colon responded to 13-norleucine motilin in concentration as low as 20 X $10^{-9}$ g per ml (page 1487, right column, lines 11-14). Further, as stated in the foregoing, Jameson et al, copy attached, describes that motilin receptors may be absent in the human colon and the therapeutic potential of erythromycin and its analogues may be limited dysmotility affecting the proximal gut only.

Moreover, to date, further documents regarding the species differences have been published. Depoortere et al (Peptides, 1991, 12, 89-94), copy attached, indicates that in rabbits motilin receptors are highly expressed in proximal colonic and distal colonic tissues (page 90, Fig. 2), while Depoortere et al (Peptides, 1993, 14, 1153-1157), copy attached, also describes that in cats, motilin receptors are not expressed in the colon at all (page 1154, Fig. 1).

Further, Yogo et al (Dig. Dis. Sci. 2007, in press), copy attached, which came to be available via Internet after the priority date of the subject application and will be published shortly, describes that in rhesus monkeys, motilin receptors are not expressed in colon (Fig. 5).

On the other hand, the subject specification discloses not only acceleratory effect of GM-116 on defecation in rabbit (Example 1) but also on that in human (Example 4). Namely, the subject specification is the first document disclosing the pharmaceutically valuable effect of GM-116 to accelerate defecation in human without changing stools into a diarrheal form. It should be noted that a medicament having such an effect has not been available for a very long time, although there has been a great need of it for treating patients with chronic constipation, such as morphine-induced constipation that often occurred in terminal stage of cancer.

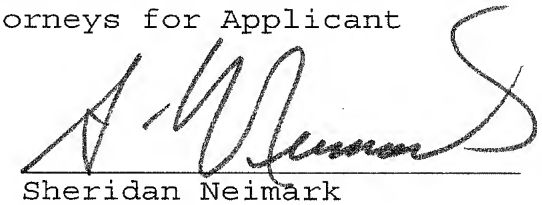
In light of the foregoing, applicants believe and strongly submit that a person skilled in the art could NOT conceive of the excellent pharmacological effect of GM-116 by referring to the two citations: Peeters and Miller, and that the present invention recited in the applicants' claims would not have been obvious to the person of ordinary skill in the art from considering the two citations.

Withdrawal of the rejection is in order and is respectfully requested.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that should lead to patentability of the present application. Favorable consideration and early formal allowance are respectfully requested.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By 
Sheridan Neimark
Registration No. 20,520

SN:kg
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YUAS\Kamei2\Pto\2007-09-18RQUSTFORRECON.doc